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THE ROLE OF FACTORS IN THE EXTERNAL ENVIRONMENT ON THE IMMUNOBIOLOGICAL REACTIVITY OF THE ORGANISM

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THE ROLE OF FACTORS IN THE EXTERNAL ENVIRONMENT ON THE IMMUNOBIOLOGICAL REACTIVITY OF THE ORGANISM

[Following is the translation of an article by V. K. Navrotskiy entitled "Rol' Faktorov Vneshney Proizvodstvennoy Sredy v Immunobiologicheskoy Reaktivnosti Organizma" (English version above) in Gigiyena Truda i Professional'nyye Zabolevaniya, Vol. ~~4~~ 3, No. 1, Moscow, 1959, pages 28-32.]

Report II. The Effect of Chronic Carbon Tetrachloride and Dichloroethane Poisoning on the Immunobiological Reactivity of Rabbits.

The present article contains the results of an investigation of immunobiological reactivity as affected by chronic intoxication with carbon tetrachloride and dichloroethane.

In this investigation we strove to attain chronic intoxication in its initial stages. The animals (rabbits) were poisoned in an inhalation chamber at a concentration of ca bon tetrachloride of 4 mg/L and 2 mg/L of dichloroethane with daily exposures of 2 hours. The animals were immunized with typhoid vaccine in three stages: an initial intravenous injection of 0.5 ml of vaccine containing 1.5 billion bacterial cells per ml and two subsequent injections of 0.8 ml of vaccine.

The time intervals between the individual injections of vaccine were established according to the period within the agglutination titer fell to the starting level. Two groups of animals were included in the experiment (with 9 to 12 rabbits in each group for each toxin). Two series of experiments were conducted with the animals, the first series consisting of preparatory intoxication with subsequent immunization and the second series of simultaneous intoxication and immunization. The control group consisted of nine animals, which were subjected to immunization alone.

In each series the following investigations were performed: the agglutination and complement titers were determined; the blood protein fraction, acetylcholine and cholinesterase activity of the blood were determined; blood and liver morphology were studied. The liver was studied for fat content alone, since this sign is specific for the

effect of chlorinated hydrocarbons of the aliphatic series. The observations were repeated every ten days.

Judging from the literature, intoxication with chlorinated hydrocarbons of the aliphatic series does not alter blood morphology. This is evidently correct with respect to the red blood cells.

Our investigations showed that the hemoglobin and erythrocyte levels seen in the case of intoxication with both toxins changed very little over a six months period, in each case not more than the change seen in the control animals, subjected to immunization alone.

At the same time, it is possible to record clear-cut changes in the white cells, characterized at times by a significant leukocytosis, while this finding was absent among the animals of the control series. In the case of carbon tetrachloride intoxication, the leukocyte count increased from 9300 to 12,000 and 14,000, and in the case of dichloroethane intoxication from 8500 to 10,500 and 12,500. Such changes in the white cells are not specific for this group of toxins. Many toxins produce such changes in the initial stages of intoxication, but subsequently, with more prolonged intoxication, the leukocyte count diminishes considerably.

We regard the leukocytosis detected in our experiments as indicative of the initial stage of chronic intoxication. This notion is supported by the fact of beginning fatty infiltration of the livers of those animals sacrificed at the conclusion of the experiment with both carbon tetrachloride and dichloroethane intoxication.

The changes in the agglutination titers are shown in Table 1.

It can be noted immediately that carbon tetrachloride and dichloroethane in the initial stage of chronic intoxication produce an abrupt depression of agglutinin formation.

Evidently this depression begins after the second month of intoxication, a fact which is evident from Table 2, which breaks the periods of intoxication into separate stages.

Confirmation of this assertion can be seen in the second series of experiments in which immunization and intoxication were performed simultaneously. In this series the agglutination titer following the first immunization (one month after intoxication) was entirely normal and was even somewhat higher than among the control animals, whereas following the second immunization (two months after intoxication) the agglutination titers were diminished in comparison with the controls by a factor of approximately

ten. Carbon tetrachloride produces significantly less depression of agglutinin formation than dichloroethane. If dichloroethane intoxication produced a depression of the agglutinin titer by a factor of 8 to 14, that produced by carbon tetrachloride was by a factor of 2 to 8. Further evidence of the greater depressive action of dichloroethane is seen in the average duration of an elevated level (relative, of course) of the agglutinin titer. If the duration of an elevated titer level in the case of carbon tetrachloride intoxication was diminished by 2 to 3 times in comparison with the control value, it was diminished by 2 to 16 times in the case of dichloroethane intoxication. Taking into account that the concentration of carbon tetrachloride to which the animals were subjected was twice as great (4 mg/L) as that of dichloroethane, one can consider the latter to be more toxic with respect to immunobiological reactivity.

Four rabbits were subjected to revaccination a month after intoxication with carbon tetrachloride had ceased, and an average maximal agglutination titer of 1:1,120 was obtained as compared with an initial level of 1:800, i.e., revaccination does not influence the immunobiological reactivity.

The complement titers (see Table 2) were normally not altered by immunization, while the complement activity of the blood diminished slightly with arbon tetrachloride intoxication and rose slightly in the case of dichloroethane intoxication. A month after cessation of the intoxication the value of the complement titer returned to the earlier level of 0.1. As the preceding investigations have shown, the complement titer is quite a stable value and can be markedly diminished only in severe intoxications.

Shifts in blood protein fractions were negligible and irregular. Normally there was a slight diminution of total proteins and albumin associated with immunization and a greater decrease in the globulin fraction, in consequence of which the A:G ration increased.

With prior CCl_4 intoxication the total protein and both fractions diminished; the A:G ratio therefore remained practically stable. With prior dichloroethane intoxication, total proteins increased through an increase in the albumin fraction; consequently the A:G ratio rose. Simultaneous intoxication and immunization produce almost no alteration in the blood protein fractions. Alterations in blood protein fractions are non-specific and, as was shown in preceding investigations, marked and stable shifts in the globulin fraction are noted with more severe intoxications

Table 1

Average values of maximal agglutination titers after immunization, normally and following intoxication.

1 Условия опыта	2 Норма			3 Отравление четыреххлористым углеродом			4 Отравление дихлорэтаном		
	5 средние величины максимальных титров агглютинации	6 колебания максимальных титров агглютинации	7 средняя длительность высокого стояния титров в днях	5 средние величины максимальных титров агглютинации	6 колебания максимальных титров агглютинации	7 средняя длительность высокого стояния титра агглютинации в днях	5 средние величины максимальных титров агглютинации	6 колебания максимальных титров агглютинации	7 средняя длительность высокого стояния титра агглютинации в днях
8 1. Предварительное отравление и последующая иммунизация									
Исходные 1	1:95	1:40—1:160	—	1:60	1:40—1:80	—	1:380	1:80—1:640	—
Период отравления 10 . .	—	—	—	1:60	1:40—1:80	—	1:160	1:80—1:320	—
1-я иммунизация 11 . .	1:8 200	1:5 120—1:20 480	37	1:1 500	1:1 280—1:2 560	12	1:1 200	1:640—1:5 120	9
2-я »	1:27 300	1:20 480—1:40 960	37	1:9 700	1:5 120—1:20 480	42	1:2 900	1:640—1:5 120	3
3-я »	1:19 300	1:19 240—1:20 480	48	1:8 500	1:5 120—1:10 240	25	1:1 300	1:640—1:2 560	3
4 **12 2. Одновременное отравление и иммунизация**									
Исходные 9	—	—	—	1:60	1:40—1:80	—	1:380	1:160—1:640	
1-я иммунизация 11 . . .	—	—	—	1:12 000	1:5 120—1:20 480	28	1:14 430	1:2 560—1:20 480	15
2-я »	—	—	—	1:2 700	1:1 280—1:5 120	22	1:2 700	1:640—1:2 560	6
3-я »	—	—	—	1:2 200	1:1 280—1:2 560	22	1:2 200	1:320—1:2 560	5

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Примечание. В каждой серии находилось 9—12 животных, средние величины максимальных титров агглютинации вычислялись из этого количест...

[Key to table on following page]

[1]Key to table 1/ 1-Experimental conditions; 2- Normal; 3-Carbon tetrachloride intoxication; 4-Dichloroethane intoxication; 5-Average values of maximal agglutination titers; 6-Fluctuations in maximal agglutination titers; 7-Average duration of elevated titer levels in days; 8-Prior intoxication and subsequent immunization; 9-Initial; 10-Period of intoxication; 11-1st immunization; 12-Simultaneous intoxication and immunization; 13-Note: In each series there were 9 to 12 animals; the average values of maximal agglutination titers were calculated from this number.

by industrial toxins. No correlation was noted between the agglutination titer and the total globulin fraction of the plasma proteins.

Just as in the preceding investigations we detected significant shifts in acetylchoine and choinesterase activity normally associated with immunizations, so too with intoxication and with intoxication and immunization together. Coincident with the appearance in the blood of acetylchoine, there was a rise in cholinesterase activity, a fact which attests to humoral compensation. It has already been shown in the preceding investigations that the appearance of aceylchoine in the blood in association with humoral compensation is a positive factor; the positive role of acetylcholine in agglutinin formation has been demonstrated earlier.

On the basis of the data obtained the conclusion can be drawn that toxins of the chlorinated hydrocarbon group of the aliphatic series even in the early stages of chronic intoxication produce a depression of immunobiologic reactivity, dichloroethane producing a greater depression than CCl_4, an effect which is associated with the physiochemical structure of this substance.

Communication I. Gigiyena trudy i professional'niye zabolyevaniya, 1957, No. 2.

Table 2

Average value of the blood complement titer, normally and after intoxication

(1) Условия опыта	Норма средней величины комплемента (2)	(3) Отравление четыреххлористым углеродом		(6) Отравление дихлорэтаном	
		средняя величина комплемента (4)	средняя длительность отравления (5)	средняя величина комплемента (6)	средняя длительность отравления (6)
	(7) А. Предварительное отравление и последующая иммунизация				
Исходные (8)	0,1	0,08	(11) — (12)	0,12	(11) — (12)
Период отравления (9)	—	0,1	1 месяц 8 дней	0,075	2 месяца 4 дня
1-я иммунизация (10)	0,1	0,09	2 месяца 5 »	0,09	4 »
2-я » (10)	0,09	0,1	4 » 5 »	0,09	5 месяцев
3-я » (10)	0,1	0,1	6 месяцев 15 »	0,09	5 » 15 дней
	(13) Б. Одновременное отравление и иммунизация				
(8) Исходные	—	0,09	(11) — (12)	0,1	(11) — (12)
1-я иммунизация (10)	—	0,1	1 месяц 11 дней	0,085	1 месяц 7 дней
2-я »	—	0,11	2 месяца 21 день	0,07	2 месяца
3-я »	—	0,11	5 месяцев 8 дней	0,09	2 » 20 дней

Key to table: 1-Experimental conditions; 2-Normal average complement level; 3-Carbon tetrachloride intoxication; 4-Average complement level; 5-Average duration of intoxication; 6-Dichloroethane intoxication; 7-Prior intoxication and subsequent immunization; 8-Initial; 9-Period of intoxication; 10-1st immunization; 11-Month; 12-Days; 13-Simultaneous intoxication and immunization.

Note: The average values of the complement titer were calculated, the minimum from 18 observations and the maximum from 66.

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